Sildenafil Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction

MeiLan K. Han, MD; David S. Bach, MD; Peter G. Hagan, MD; Eric Yow, MS; Kevin R. Flaherty, MD, FCCP; Galen B. Toews, MD; Kevin J. Anstrom, PhD; and Fernando J. Martinez, MD, FCCP; for the IPFnet Investigators*

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with pulmonary vasculopathy.

Objective: The purpose of this study was to determine whether sildenafil improves 6-min walk distance (6MWD) in subjects with IPF and right ventricular dysfunction.

Methods: The IPFnet, a network of IPF research centers in the United States, conducted a randomized trial examining the effect of sildenafil on 6MWD in patients with advanced IPF, defined by carbon monoxide diffusing capacity <35% predicted. A substudy examined 119 of 180 randomized subjects where echocardiograms were available for independent review by two cardiologists. Right ventricular (RV) hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed. Multivariable linear regression models estimated the relationship between RV abnormality, sildenafil treatment, and changes in 6MWD, St. George's Respiratory Questionnaire (SGRQ), the EuroQol instrument, and SF-36 Health Survey (SF-36) from enrollment to 12 weeks.

Results: The prevalence of RVH and RVSD were 12.8% and 18.6%, respectively. RVSP was measurable in 71 of 119 (60%) subjects; mean RVSP was 42.5 mm Hg. In the subgroup of subjects with RVSD, subjects treated with sildenafil experienced less decrement in 6MWD (99.3 m; $P = .01$) and greater improvement in SGRQ (13.4 points; $P = .005$) and EuroQol visual analog scores (17.9 points; $P = .04$) than subjects receiving placebo. In the subgroup with RVH, sildenafil was not associated with change in 6MWD ($P = .13$), but was associated with greater relative improvement in SGRQ (14.8 points; $P = .02$) vs subjects receiving placebo. Sildenafil treatment in those with RVSD and RVH was not associated with change in SF-36.

Conclusions: Sildenafil treatment in IPF with RVSD results in better preservation of exercise capacity as compared with placebo. Sildenafil also improves quality of life in subjects with RVH and RVSD.

CHEST 2013; 143(6):1699–1708

Abbreviations: 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; DLCO = carbon monoxide diffusing capacity; IPF = idiopathic pulmonary fibrosis; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; QOL = quality of life; RHC = right-sided heart catheterization; RV = right ventricular; RVH = right-sided ventricular hypertrophy; RVSD = right-sided ventricular systolic dysfunction; RVSP = right-sided ventricular systolic pressure; SF-36 = Short-Form 36 Health Survey; SGRQ = St George's Respiratory Questionnaire; STEP-IPF = Sildenafil Trial of Exercise Performance in IPF; WHO = World Health Organization

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disorder of unknown etiology with no clearly efficacious therapies to alter disease progression or mortality. Pulmonary hypertension (PH) in IPF has been previously reported, particularly in patients with advanced disease.¹ This is likely due to a combination of aberrant vascular remodeling, fibrotic destruction of the vasculature, and hypoxic vasoconstriction.² Sildenafil,

a phosphodiesterase-5 inhibitor, is a pulmonary-selective vasodilator that has previously been documented to improve exercise capacity and hemodynamics in symptomatic subjects with idiopathic pulmonary arterial hypertension (PAH), PAH associated with connective tissue disease, or PAH following surgical repair of left-to-right congenital heart lesions.³ However, two small, prior clinical trials suggested a possible

role for sildenafil in IPF. The first study identified subjects with concomitant PH on right-sided heart catheterization (RHC) and demonstrated pulmonary vasodilation and improved gas exchange in 16 subjects after acute challenge with sildenafil as compared with IV epoprostenol.⁴ A second, small, open-label study of patients with IPF and with PH on echocardiography or RHC showed improvement in 6-min walk distance (6MWD) after 3 months of sildenafil.⁵ Consequently, we performed the Sildenafil Trial of Exercise Performance in IPF (STEP-IPF) study, a double-blind, placebo-controlled study in 180 patients with advanced IPF. We hypothesized sildenafil would improve exercise tolerance, reduce dyspnea, and improve quality of life (QOL).⁶ This trial showed statistically significant differences in dyspnea and QOL with sildenafil treatment. However, the primary end point of 20% improvement in 6MWD with sildenafil treatment (10% vs 7%; $P = .39$) was not met.

Prior work suggests a third to half of patients with advanced IPF evaluated for lung transplantation demonstrate PH, whether assessed by echocardiogram or RHC.^{7,8} PH in IPF has been associated with worse survival.^{8,9} Sildenafil improves exercise tolerance in World Health Organization (WHO) group 1 PAH¹⁰; therefore, we hypothesized that PH evident on echocardiogram would predict response to sildenafil in the STEP-IPF trial. There are no US Food and Drug Administration-approved therapies demonstrated to modify the disease course, so a treatment that could preserve exercise capacity and QOL in IPF patients with PH would be valuable. Here we examine the subset of STEP-IPF subjects who had baseline echocardiograms available for independent review to assess for right-sided ventricular (RV) abnormalities and their relationship to changes in exercise performance and

QOL. An abstract representing a portion of these analyses was previously published.^{11,12}

MATERIALS AND METHODS

Setting and Participants

The complete STEP-IPF protocol has been previously published.⁶ See e-Appendix 2 for a full description of the study methods. This was a double-blind, placebo-controlled trial of sildenafil in patients with advanced IPF and was conducted at 14 IPFnet centers (e-Appendix 1). All subjects provided written informed consent. The study was approved by institutional review boards at participating institutions. Eligibility criteria included consensus criteria-defined IPF and carbon monoxide diffusing capacity (DLCO) <35% predicted. Resting oxygen saturation <92% on 6 L of supplemental oxygen, aortic stenosis, idiopathic hypertrophic subaortic stenosis, or severe heart failure (left-sided ventricular ejection fraction <25%) were additional exclusion criteria. Oral sildenafil (20 mg tid) was administered in a double-blind, randomized, placebo-controlled fashion. The study consisted of two periods. The first period was a 12-week, double-blind, placebo-controlled study of sildenafil. The second period was a 12-week, open-label extension. Results reported here are from the first period.

Outcomes and Follow-up

For this separately funded substudy, echocardiograms were transferred to the University of Michigan for independent review (see e-Appendix 2 for full echocardiogram protocol). All echocardiograms were performed prior to randomization and scored independently and in a blinded fashion by two cardiologists with advanced expertise in echocardiography. All subjects for whom baseline echocardiogram was available for central review were included in this substudy. Right-sided ventricular hypertrophy (RVH) was graded as present or absent based on increased free-wall thickness (>5 mm) or prominent and hypertrophied trabeculae. For these analyses, any level of abnormality in RV systolic function was classified as dysfunction. As brain natriuretic peptide (BNP) has been suggested as a noninvasive marker for PH in IPF,¹³ BNP was also measured at enrollment.

Statistical Analysis

All analyses were performed using SAS 9.2 (SAS Institute Inc). Baseline comparisons used χ^2 tests for categorical variables and Wilcoxon tests for continuous variables. Linear regression models estimated changes in outcome variables as functions of treatment group, cardiac parameters, and interactions between treatment group and cardiac parameters. A sensitivity analysis was conducted to determine if differences in the echocardiogram substudy population as compared with the entire population contributed to the differences in 6MWD change using inverse probability-weighted estimators. A logistic regression model (propensity score model) was constructed with the response variable of echocardiogram availability. The estimated propensity scores were used to construct weights that were applied to the standard linear regression models for change in 6MWD.

RESULTS

Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, $n = 56$; placebo, $n = 63$) (Fig 1).

Manuscript received July 16, 2012; revision accepted December 1, 2012.

Affiliations: From the University of Michigan Health System (Drs Han, Bach, Hagan, Flaherty, Toews, and Martinez), Ann Arbor, MI; and Duke Clinical Research Institute (Mr Yow and Dr Anstrom), Durham, NC.

*A complete list of study participants is located in e-Appendix 1.

Funding/Support: This work is supported by funding from National Institutes of Health/National Heart, Lung and Blood Institute [Grants K23 HL093351 and U10HL080509 (data coordinating center), U10HL80413, U10HL80274, U10HL80370, U10HL80371, U10HL80383, U10HL80411, U10HL80509, U10HL80510, U10HL80513, U10HL80543, U10HL80571, and U10HL80685 (clinical centers)]; by the Cowlin Fund at the Chicago Community Trust; by Pfizer Inc, which donated sildenafil and matching placebo; and by Masimo Corp, which donated pulse oximeters.

Correspondence to: MeiLan K. Han, MD, Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, 3916 Taubman Center, Box 5360, 1500 E Medical Center Dr, Ann Arbor, MI 48109-5360; e-mail: mrking@umich.edu

© 2013 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.12-1594

FIGURE 1. Consolidated Standards of Reporting Trials Diagram.

The remaining 61 echocardiograms could not be transferred to the echocardiogram core for review due to inability of clinical centers to obtain institutional review board permission for data transfer. No significant difference was detected in the high-resolution CT image scoring or pathology scoring for patients treated with sildenafil vs placebo (e-Table 1). In examining subjects for whom echocardiogram was available

for review vs those with unavailable echocardiogram, no significant difference was seen in smoking history, lung function, or 6MWD (Table 1). Subjects with echocardiograms available for review were slightly younger, (mean age, 67.7 vs 71.3 years; $P = .01$) and were more recently diagnosed with IPF (1.67 vs 2.49 years from diagnosis; $P = .006$). No significant difference in subjects with echocardiograms stratified by treatment status was seen (e-Table 2).

Baseline echocardiogram data are presented in Table 2. There were no significant differences in chamber size or function between subjects treated with sildenafil and those treated with placebo. Right-sided atrial size abnormality of any severity was detected in 36.9% of subjects, RVH was present in 12.8% of subjects (nine treated with sildenafil and six with placebo), and RV systolic dysfunction (RVSD) of any severity was noted in 18.6% of subjects (11 per treatment arm). All but one subject with RVH also had RVSD. There was 100% interobserver agreement between the cardiologists in determining the presence of RVH. While there was not complete interobserver agreement regarding severity of RVSD, there was 100% agreement that some level of RVSD was present. For these analyses, subjects with any severity of RVSD were grouped. RVH could not be assessed in two subjects and RVSD could not be assessed in one subject due to inadequate visualization. RV systolic pressure (RVSP) was measureable in 71 of 119 (59.7%) subjects. Mean RVSP for the entire group was 42 mm Hg. Interobserver agreement within 5 mm Hg for the measurement of RVSP was 68.1%, although values differed by > 10 mm Hg in only one instance. The prevalence of abnormal left-sided ventricular systolic dysfunction was very low (1.7%).

A series of multivariable models were constructed to determine the relationship between cardiac abnormality, treatment, and change in outcome of interest. We performed contrast tests for subgroup comparisons: $\Delta 6\text{MWD}_{\text{sildenafil/RVSD}+} - \Delta 6\text{MWD}_{\text{placebo/RVSD}+}$, where $\Delta 6\text{MWD}$ is change in 6MWD from baseline to 12 weeks, $\text{RVSD}+$ identifies a subset of patients with RVSD, and RVSD^- identifies a subset of patients without RVSD. This informs us about differences in effect of sildenafil vs placebo in the subgroup of patients with RVSD. We also report significance for the interaction terms in the model. This addresses whether the combination of cardiac abnormality and treatment with sildenafil has a more than additive effect on the outcome of interest: $(\Delta 6\text{MWD}_{\text{sildenafil/RVSD}+} - \Delta 6\text{MWD}_{\text{placebo/RVSD}+}) - (\Delta 6\text{MWD}_{\text{sildenafil/RVSD}^-} - \Delta 6\text{MWD}_{\text{placebo/RVSD}^-})$.

Table 3 shows analyses examining change in 6MWD at 12 weeks. A statistically significant interaction between sildenafil treatment and RVSD was detected ($P = .04$), suggesting that sildenafil in the presence of RVSD has a more than additive effect on 6MWD.

Table 1—Demographic Data Stratified by Echocardiogram Status

Characteristics	Echocardiogram Cohort (n = 119)	No Echocardiogram Cohort ^a (n = 61)	P Value
Age, y	67.7	71.4	.01
FVC % predicted, %	56.9	56.8	.83
DLCO% predicted, %	26.0	26.7	.40
Smoking status			
Current, no. (%)	0 (0.0)	0 (0.0)	.87
Past, no. (%)	91 (76.5)	46 (75.4)	
Never, no. (%)	28 (23.5)	15 (24.6)	
Duration of IPF fibrosis, y	1.7	2.5	.006
PO ₂ , mean, mm Hg	68.6	67.1	.52
PCO ₂ , mm Hg	38.7	40.4	.08
Arterial alveolar gradient	28.5	30.5	.23
6MWD, m	273.4	248.8	.14

Data for continuous variables are given as the mean unless otherwise indicated. 6MWD = 6-min walk distance; DLCO% = carbon monoxide diffusion capacity; IPF = idiopathic pulmonary fibrosis; PO₂ = partial pressure of oxygen.

^aThese subjects had an echocardiogram for the STEP-IPF trial. However, they were not included in the echocardiogram substudy cohort due to inability to transfer data to the echocardiogram core for review.

Table 2—Cardiac Parameters

Parameters	Sildenafil	Placebo	All Echocardiogram Patients	P Value ^a
Right-side atrial size				.50
Normal	33/56 (58.9)	42/63 (66.7)	75/119 (63.0)	
Mild to moderate	22/56 (39.3)	21/63 (33.3)	43/119 (36.1)	
Severe	1/56 (1.8)	0/63 (0)	1/119 (0.8)	
Right atrial pressure				.17
5 mm Hg	36/56 (64.3)	50/63 (79.4)	86/119 (72.3)	
10 mm Hg	17/56 (30.4)	12/63 (19.0)	29/119 (24.4)	
15 mm Hg	3/56 (5.4)	1/63 (1.6)	4/119 (3.4)	
Right ventricular hypertrophy				.28
Absent	46/55 (83.6)	56/62 (90.3)	102/117 (87.2)	
Present	9/55 (16.4)	6/62 (9.7)	15/117 (12.8)	
Right ventricular systolic function				.80
Normal	45/56 (80.4)	51/62 (82.3)	96/118 (81.4)	
Abnormal	11/56 (19.6)	11/62 (17.7)	22/118 (18.6)	
Right ventricular systolic pressure measureable	35/56 (62.5)	36/63 (57.1)	71/119 (60.0)	.55
Right ventricular systolic pressure (mm Hg)	43 (16)	42 (16)	42 (16)	.65
Left ventricular systolic function				
Normal	55/56 (98.2)	62/63 (98.4)	117/119 (98.3)	>.99
Abnormal	1/56 (1.8)	1/63 (1.6)	2/119 (1.7)	
Brain natriuretic peptide	79.1	66.2	72.2	.82

Data presented as no. patients/total patients (%), unless otherwise indicated.

^aP value is for comparison between placebo and sildenafil groups.

While on average, 6MWD declined over the course of 12 weeks for all subjects, those with any evidence of RVSD treated with sildenafil demonstrated a 99.3 m greater 6MWD as compared with those treated with placebo ($P = .01$) (Fig 2). Those without RVH treated with sildenafil did not demonstrate a significant change in 6MWD as compared with placebo ($P = .13$) (Fig 3). The model containing inverse probability-weighted estimates adjusting for differences in the population of patients with echocardiogram data vs those without did not materially change the results of the change in 6MWD models. These data are additionally presented in spaghetti plot form in e-Figures 1 and 2, which add to our understanding of the data. Here we see that subjects with cardiac abnormality tended to have the most pronounced declines in 6MWD over the 12-week period. This decline appears to be mitigated to slightly improved with sildenafil treatment.

We also explored whether RVSP or BNP predicted treatment response with respect to 6MWD, but no significant interaction was detected in either case ($P = .27$ and $P = .24$, respectively). Neither was a significant treatment interaction detected for RVSP > 40 mm Hg or > 50 mm Hg with respect to change in 6MWD ($P = .18$ and $P = .14$, respectively). Mortality by cardiac and treatment status is shown in e-Table 3. The groups are too small to compare statistically; however, no deaths occurred in patients with RVH and RVSD who were on treatment. One death occurred in each of the RVH and RVSD subgroups on placebo.

The relationship between treatment, cardiac abnormality, and QOL changes were also examined (Tables 4 and 5, Figs 2-4). The original STEP-IPF analyses demonstrated improvements in St George's Respiratory Questionnaire (SGRQ) scores with sildenafil treatment in all subjects: total, 4.1 ($P = .01$); symptoms,

Table 3—Contrast Tests Comparing Effect of Sildenafil vs Placebo in Subjects With and Without RVH and RVSD on Change in 6MWD at 12 Wk

Subgroup	Estimate for Difference in 6MWD Between Treatment Groups ^a , m	95% CI	P Value for Contrast Test ^a	P Value for Interaction ^b
Sildenafil with no RVH vs placebo with no RVH	19.1	−18.1 56.4	.31	.28
Sildenafil with RVH vs placebo with RVH	78.5	−24.1 181.0	.13	
Sildenafil with no RVSD vs placebo with no RVSD	10.0	−27.9 47.8	.60	.04
Sildenafil with RVSD vs placebo with RVSD	99.3	22.3 176.2	.01	

RVH = right-sided ventricular hypertrophy; RVSD = right-sided ventricular systolic dysfunction.

^aEstimate represents change in 6MWD between 0 and 12 wk for each treatment group. For example, the difference in 12-wk change between subjects with RVSD who treated with sildenafil vs subjects with RVSD who were treated with placebo was 99.3 m ($\Delta 6\text{MWD}_{\text{sildenafil}+/ \text{RVSD}+} - \Delta 6\text{MWD}_{\text{placebo}/ \text{RVSD}+} = 99.3 \text{ m}$). The P value for contrast test corresponds to this comparison.

^b P value for interaction addresses whether the combination of cardiac abnormality and treatment with sildenafil has a more than additive effect on the outcome of interest, ($\Delta 6\text{MWD}_{\text{sildenafil}+/ \text{RVSD}+} - \Delta 6\text{MWD}_{\text{placebo}/ \text{RVSD}+}$) − ($\Delta 6\text{MWD}_{\text{sildenafil}+/ \text{RVSD}-} - \Delta 6\text{MWD}_{\text{placebo}/ \text{RVSD}-}$).

FIGURE 2. Change in 6MWD at 12 weeks by treatment and presence of RVSD. + = mean. The box represents the 25th-75th percentiles. The line within the box is the 50th percentile. The upper and lower hinges represent the minimum and maximum values. Higher values indicated improvement. 6MWD = 6-min walk distance; RVSD = right-sided ventricular systolic dysfunction.

5.7; ($P = .02$); and activity, 3.6 ($P = .04$). Here we demonstrate a significant interaction between RVSD and both SGRQ total and symptoms scores ($P = .048$ and

0.002, respectively), suggesting even greater QOL improvements in patients with RVSD who were treated with sildenafil. Contrast tests confirmed treatment

FIGURE 3. Change in 6MWD at 12 weeks by treatment and presence of RVH. + = mean. The box represents the 25th-75th percentiles. The line within the box is the 50th percentile. The upper and lower hinges represent the minimum and maximum values. Higher values indicated improvement. RVH = right-sided ventricular hypertrophy. See Figure 2 legend for expansion of other abbreviations.

Table 4—Contrast Tests Comparing Effect of Sildenafil vs Placebo in Subjects With and Without RVH on Change in QoL Measures at 12 Wk

QoL Measures by Treatment Group	12-wk Change Estimate in Points ^a	95% CI		P Value for Contrast Test ^a	P Value for Interaction ^b
EuroQoL self-report questionnaire change					
Sildenafil with no RVH vs placebo with no RVH	−0.02	−0.10	0.07	.69	.09
Sildenafil with RVH vs placebo with RVH	0.19	−0.03	0.41	.09	
EuroQoL VAS change					
Sildenafil with no RVH vs placebo with no RVH	1.8	−6.6	10.2	.68	.98
Sildenafil with RVH vs placebo with RVH	1.5	−21.6	24.5	.90	
SGRQ symptoms change					
Sildenafil with no RVH vs placebo with no RVH	−6.1	−12.8	0.6	.08	.09
Sildenafil with RVH vs placebo with RVH	−23.1	−41.2	−4.9	.01	
SGRQ activity change					
Sildenafil with no RVH vs placebo with no RVH	−4.6	−9.5	0.4	.07	.60
Sildenafil with RVH vs placebo with RVH	−0.7	−14.5	13.1	.92	
SGRQ impacts change					
Sildenafil with no RVH vs placebo with no RVH	−1.7	−7.1	3.8	.55	.02
Sildenafil with RVH vs placebo with RVH	−20.3	−35.3	−5.3	.009	
SGRQ total change					
Sildenafil with no RVH vs placebo with no RVH	−3.4	−7.8	1.0	.13	.08
Sildenafil with RVH vs placebo with RVH	−14.8	−26.8	−2.8	.02	
SF-36 physical change					
Sildenafil with no RVH vs placebo with no RVH	−0.7	−3.1	1.7	.54	.47
Sildenafil with RVH vs placebo with RVH	1.8	−4.6	8.2	.58	
SF36 mental change					
Sildenafil with no RVH vs placebo with no RVH	0.7	−3.2	4.6	.73	.78
Sildenafil with RVH vs placebo with RVH	2.2	−8.2	12.6	.67	

QoL = quality of life; SF-36 = Short-Form 36 Health Survey; SGRQ = St George's Respiratory Questionnaire; VAS = visual analog scale. See Table 3 legend for expansion of other abbreviations.

^aEstimate represents change in quality of life measure between 0 and 12 wk for each treatment group. Points are relative to each QoL measure analyzed. *P* value for contrast test corresponds to this comparison.

^b*P* value for interaction addresses whether the combination of cardiac abnormality and treatment with sildenafil has a more than additive effect on the outcome of interest.

with sildenafil in subjects with RVSD resulted in a 13.4-point relatively lower SGRQ total score ($P = .005$) and 28.0-point relatively lower SGRQ symptoms score ($P < .0001$). For other QOL indices, contrast tests confirmed subjects with RVSD treated with sildenafil still experienced better outcomes than those treated with placebo, including a 14.0-point relatively lower SGRQ impact score ($P = .02$) (Fig 4) and a 17.9-point relatively higher EuroQol visual analog score ($P = .04$) comparing sildenafil to placebo, although the *P* value for interaction for these comparisons was not statistically significant, indicating similar improvement in those with and without RVSD.

Similarly, contrast tests also demonstrated statistically and clinically significant improvements in QOL indices for subjects with RVH who were treated with sildenafil (Fig 5): a 14.8-point relatively lower SGRQ total score ($P = .02$), 23.1-point relatively lower SGRQ symptoms score ($P = .01$), and a 20.3-point relatively lower SGRQ impacts score ($P = .009$); however, the interaction test *P* value was not significant, indicating treatment effect of sildenafil was not statistically different between those subjects with and without RVH. No significant change for SGRQ activity score, EuroQol

self-report questionnaire, or Short-Form 36 Health Survey (SF-36) scores were seen in contrast tests comparing sildenafil to placebo in patients with either RVSD or RVH.

DISCUSSION

We have demonstrated that sildenafil treatment results in significantly better exercise capacity and QOL in IPF for subjects with RVSD present on echocardiogram. It has previously been demonstrated that PH results in exercise limitation in patients with IPF.¹⁴ Prior work suggests that sildenafil leads to preferential pulmonary artery vasodilation in well-ventilated lung tissue and may improve ventilation-perfusion matching and gas exchange in IPF.⁴ Hence, STEP-IPF hypothesized that sildenafil treatment would improve exercise capacity in advanced IPF. Here we identified a clinically significant effect in a subgroup of that population with RVSD on echocardiogram. The difference in 6MWD detected between those with and without RVSD between treatment groups was approximately 99 m, exceeding the minimum important difference for 6MWD in IPF estimated to be 24–45 m.¹⁵

Table 5—Contrast Tests Demonstrating Significance of Interactions Between Treatment and Presence of RVSD on Change in QOL Measure at 12 Wk

QoL Measures by Treatment Group	12-wk Change Estimate in Points ^a	95% CI		P Value for Contrast Test ^a	P Value for Interaction ^b
EuroQoL self-report questionnaire change					
Sildenafil with no RVSD vs placebo with no RVSD	−0.02	−0.11	0.06	.56	.05
Sildenafil with RVSD vs placebo with RVSD	0.16	−0.01	0.33	.06	
EuroQoL VAS change					
Sildenafil with no RVSD vs placebo with no RVSD	−1.4	−10.0	7.1	.74	.05
Sildenafil with RVSD vs placebo with RVSD	17.9	0.6	35.3	.04	
SGRQ symptoms change					
Sildenafil with no RVSD vs placebo with no RVSD	−3.8	−10.7	3.0	.27	.002
Sildenafil with RVSD vs placebo with RVSD	−28.0	−41.7	−14.4	<.0001	
SGRQ activity change					
Sildenafil with no RVSD vs placebo with no RVSD	−4.1	−9.2	1.1	.12	.80
Sildenafil with RVSD vs placebo with RVSD	−5.6	−16.1	5.0	.30	
SGRQ impacts change					
Sildenafil with no RVSD vs placebo with no RVSD	−1.8	−7.5	3.9	.53	.07
Sildenafil with RVSD vs placebo with RVSD	−14.0	−25.6	−2.4	.02	
SGRQ total change					
Sildenafil with no RVSD vs placebo with no RVSD	−3.0	−7.6	1.7	.20	.048
Sildenafil with RVSD vs placebo with RVSD	−13.4	−22.7	−4.2	.005	
SF36 physical change					
Sildenafil with no RVSD vs placebo with no RVSD	−0.9	−3.4	1.6	.47	.40
Sildenafil with RVSD vs placebo with RVSD	1.4	−3.5	6.3	.56	
SF36 mental change					
Sildenafil with no RVSD vs placebo with no RVSD	0.5	−3.5	4.6	.79	.43
Sildenafil with RVSD vs placebo with RVSD	4.1	−3.9	12.1	.31	

See Tables 3 and 4 legends for expansion of other abbreviations.

^aEstimate represents change in QOL measure between 0 and 12 wk for each treatment group. Points are relative to each quality of life measure analyzed.

^bP value for interaction addresses whether the combination of cardiac abnormality and treatment with sildenafil has a more than additive effect on the outcome of interest.

While RVH data trended in the same direction, differences were not statistically significant. Very few patients met criteria for RVH (12.8%) and a larger number met criteria for RVSD (18.6%), so the study may have been underpowered to detect a treatment difference in subjects with RVH.

This benefit for subjects with RVSD can be largely attributed to the fact that this subgroup also experiences the most rapid declines in 6MWD, which appears to be mitigated by sildenafil.

In comparison with trials of sildenafil in WHO group 1 patients, disease differences such as the presence of fibrosis, as well as potential local areas of V/Q mismatching present in IPF, likely influence differences in the magnitude of response to sildenafil. In addition, differences in the age and functional status of the two patient groups may also contribute to differences in response.

We also report improvements in QOL. Sildenafil treatment in the original STEP study resulted in a 4.1-point improvement in total SGRQ score. The minimal important difference for SGRQ in IPF has been estimated at 5-8 points.¹⁶ This analysis demonstrates even greater improvements with sildenafil treatment in those with RVSD: 13.4-, 14.0-, and 28.0-point

better SGRQ total, impacts, and symptoms scores, respectively, mirroring improvements in exercise capacity. Among those with RVSD, sildenafil also resulted in a 17-point difference in the EuroQol visual analog scale ($P = .04$) and a 0.16-point difference in the self-report questionnaire ($P = .06$) as compared with placebo. The minimal important difference for this instrument has been estimated at 7 points for the visual analog scale and 0.08 points for the self-report questionnaire, although these estimates were made in cancer, not IPF.¹⁷ Those with RVH treated with sildenafil demonstrated a 14.8-point improvement in SGRQ score, although the interaction was not significant, suggesting we cannot say differences in this subgroup are significantly different from all subjects treated with sildenafil. While neither RVSD nor RVH predicted treatment related changes in SF-36, the SGRQ and EuroQol may be more sensitive to short-term QOL changes than the SF-36 in IPF.

The most notable other trials of vasodilator therapies in IPF evaluated bosentan, an endothelin receptor antagonist with vasodilatory and antifibrotic properties, currently approved to treat WHO group 1 PH. In the first of two studies (BUILD-1; Bosentan Use in Interstitial Lung Disease), bosentan did not improve 6MWD,

FIGURE 4. Change in SGRQ total score at 12 weeks by treatment and presence or RVSD. + = mean. The box represents the 25th-75th percentiles. The line within the box is the 50th percentile. The upper and lower hinges represent the minimum and maximum values. Lower values indicated improvement. SGRQ = St George's Respiratory Questionnaire. See Figure 1 and 2 legends for expansion of other abbreviations.

although a trend toward QOL improvement and delayed time to death was seen.¹⁸ A follow-up study (BUILD-3) was conducted in patients with milder disease.¹⁹ However, the primary end point of delay in IPF worsening or death was not met with no changes in 6MWD or QOL. Drug mechanism of action may have contributed to differences in results in the BUILD studies as compared with ours. Bosentan is a dual endothelin receptor antagonist, whereas sildenafil is a phosphodiesterase-5 inhibitor. Endothelin-1 is a potent vasoconstrictor. While endothelin-1 has been reported to be elevated in IPF and correlates with higher pulmonary arterial pressures, it has also been demonstrated that the relationship is nonlinear, with only a subgroup of patients demonstrating correlations between higher levels of endothelin-1 and pulmonary arterial pressures.²⁰ Hence, it is possible that the mechanism for vasodilation with bosentan is less broadly applicable in IPF, contributing to differences in study results. Additionally, however, BUILD-1 excluded subjects with evidence of severe PH on echocardiogram. BUILD-3 subjects also had milder disease severity. Even in the patient population with advanced IPF, the prevalence of patients with RVSD was low. Consequently, the presence of RVSD was likely very low in both the BUILD and IPF populations.

The prevalence of RV abnormality in our study was low despite having a DLCO < 35% inclusion criteria.

It should be noted that patients with significant left ventricular dysfunction were excluded from this trial. There is a known, but imperfect, inverse correlation between DLCO% predicted and PH.²¹ Nadrous et al²² previously reported on 88 patients with IPF who were stratified by RVSP. Forty-seven subjects had an RVSP 35-50 mm Hg (mean, 43 mm Hg), which is comparable to our series. In that series (n = 47), 5 of 47 patients (10.6%) had any RV size abnormalities and 2 of 47 (4.3%) had any RV function abnormality. However, the mean DLCO% predicted for this group was 54.3%. For those with RVSP > 50 mm Hg, mean DLCO% predicted was 38.8%, with 12 of 27 (44.4%) subjects with RV size abnormality and 8 of 27 (29.6%) subjects with RV function abnormality. Hence, the prevalence of RVSD and RVH in STEP-IPF is within the range found in prior reports, but, in general, was still low despite the inclusion criteria of DLCO < 35% predicted.

Our study has several limitations. echocardiograms were not available in all subjects due to inability to obtain permissions to transfer echocardiograms for central interpretation. However, as echocardiograms were performed prior to randomization and these problems occurred at the clinical center level, we do not believe this introduced systematic bias. Furthermore, we have not detected any significant difference in subject lung function or 6MWD between subjects

FIGURE 5. Change in SGRQ total score at 12 weeks by treatment and presence or RVH. + = mean. The box represents the 25th-75th percentiles. The line within the box is the 50th percentile. The upper and lower hinges represent the minimum and maximum values. Lower values indicated improvement. See Figure 3 and 4 legends for expansion of abbreviations.

with vs without echocardiograms available. This is a retrospective analysis. The number of subjects with significant right-sided heart abnormality was also small and as such may not be representative of this patient population at large. It is possible that the limited effects for sildenafil found in the STEP-IPF study may be due to the relatively small number of subjects with RV dysfunction (11 subjects per treatment arm). Any study demonstrating treatment effect in a small group of subjects will inherently be more subject to bias from differences in the underlying characteristics of the patient populations. Whether RHC data would provide even better discriminatory ability is unknown and opens the door for potential future investigations. We know that the correlation between pulmonary arterial pressures assessed via echocardiogram vs catheterization is modest; the sensitivity of echocardiogram is approximately 75% to 85% and the specificity 20% to 50% for detecting PH as compared with RHC.²³ However, the data from the current study suggest echocardiogram is useful for identifying a subset of patients with IPF who experience better exercise capacity and QOL with sildenafil therapy. Finally, the durability of effect is unknown and will also need further prospective evaluation.

In summary, we extend results of STEP-IPF where improvements in arterial oxygenation, dyspnea, and QOL in patients with IPF and DLCO < 35% who were treated with sildenafil were demonstrated. Our

findings suggest that in advanced IPF, the subgroup of patients with right-sided heart abnormality diagnosed via echocardiogram is at significant risk for declines in functional capacity as evidenced by the rapid deterioration in the patients treated with placebo in this subgroup. However, we also have the potential to significantly impact this subgroup through targeted treatment of PH with sildenafil, which, in this analysis, resulted in maintenance of exercise capacity and improvements in QOL.

ACKNOWLEDGMENTS

Author contributions: Drs Han and Anstrom had full access to all of the data and take responsibility for the integrity and accuracy of the data analysis.

Dr Han: contributed to study conception and design; data collection, analysis, and interpretation; writing of the manuscript; and served as principal author.

Dr Bach: contributed to data analysis and interpretation, and writing of the manuscript.

Dr Hagan: contributed to data analysis and interpretation, and writing of the manuscript.

Mr Yow: contributed to data collection, analysis and interpretation, and writing of the manuscript.

Dr Flaherty: contributed to study conception and design; data collection and interpretation; and writing of the manuscript.

Dr Toews: contributed to study conception and design; data interpretation; and writing of the manuscript.

Dr Anstrom: contributed to study conception and design; data collection, analysis, and interpretation; and writing of the manuscript.

Dr Martinez: contributed to study conception and design; data collection and interpretation; and writing of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Han has participated

in advisory boards for Boehringer Ingelheim GmbH, Pfizer Inc, GlaxoSmithKline plc, Genentech, Inc, Novartis AG, Forest Laboratories, Inc, and MedImmune, LLC. She has participated on speaker's bureaus for Boehringer Ingelheim GmbH, Pfizer Inc, GlaxoSmithKline plc, the National Association for Continuing Education, Grifols and Forest Laboratories, Inc, and WebMD LLC. She has consulted for Novartis AG, Ikaria, Inc, United BioSource Corporation, and Nycomed International Management GmbH (now Takeda Pharmaceuticals International GmbH), and has received royalties from UpToDate Inc and Epocrates, Inc. Dr Flaherty has received research support from the National Institutes of Health, InterMune, and Centocore Biotech, Inc (now Janssen Biotech Inc). He has consulted for FibroGen Inc, Gilead Sciences, Inc, and Boehringer Ingelheim GmbH. He has participated on speaker's bureaus for GlaxoSmithKline plc and Boehringer Ingelheim GmbH, and has received royalties from UpToDate, Inc. Dr Martinez has participated in advisory boards covering COPD or IPF topics for ABLE Associates, Actelion Pharmaceuticals, Ltd, Almirall, SA, Bayer AG, GlaxoSmithKline plc, Ikaria, Inc, Janssen Pharmaceuticals, Inc, MedImmune, LLC, Merck & Co, Inc, Pearl, Pfizer Inc, and Vertex Pharmaceuticals Incorporated. He has consulted on COPD or IPF topics for American Institutes for Research, AstraZeneca, Bayer AG, Carden Jennings Publishing Co., Ltd, CardioMEMS, Grey Healthcare Group, HealthCare Research and Consulting, Janssen, Merion, Nycomed (now Takeda Pharmaceuticals International GmbH), and Sudler and Hennessey. He has been a member of steering committees for studies sponsored by Actelion Pharmaceuticals, Ltd, Janssen Biotech, Inc., Forest Pharmaceuticals, Inc, GlaxoSmithKline plc, Gilead, Mpex, Nycomed (now Takeda Pharmaceuticals International GmbH). He has participated in Food and Drug Administration mock panels for Boehringer Ingelheim GmbH and Forest Pharmaceuticals, Inc. The University of Michigan received funds from the National Institutes of Health for COPD and IPF studies. He has served on speaker's bureaus or in continuing medical education activities sponsored by American College of Chest Physicians; American Lung Association, AstraZeneca, Bayer AG, William Beaumont Hospital, Boehringer Ingelheim GmbH, Center for Health Care Education, CME Incite, Forest Pharmaceuticals, The France Foundation, GlaxoSmithKline plc, Lovelace Health System, MedEd, MedScape/WebMD LLC, National Association for Continuing Education Inc., CME Networks, LLC, Nycomed (now Takeda Pharmaceuticals International GmbH), Projects in Knowledge, Inc, St Luke's Health System, the University of Illinois at Chicago College of Medicine, University of Texas Southwestern, University of Virginia, and UpToDate, Inc. He has served on DSMBs for Biogen and Novartis Corporation. He has received royalties from Castle Connolly Medical Ltd and Informa plc. All other authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Additional information: The e-Appendixes, e-Tables, and e-Figures can be found in the "Supplemental Materials" area of the online article.

REFERENCES

- Weitzenblum E, Ehrhart M, Rasaholjanahary J, Hirth C. Pulmonary hemodynamics in idiopathic pulmonary fibrosis and other interstitial pulmonary diseases. *Respiration*. 1983; 44(2):118-127.
- Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. *Chest*. 2007; 132(3):998-1006.
- Galiè N, Ghofrani HA, Torbicki A, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353(20):2148-2157.
- Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet*. 2002;360(9337):895-900.
- Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest*. 2007;131(3):897-899.
- Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med*. 2010;363(7): 620-628.
- Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med*. 2003;167(5): 735-740.
- Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest*. 2006; 129(3):746-752.
- Nadrous HF, Pellikka PA, Krowka MJ, et al. The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis. *Chest*. 2005;128(suppl 6):616S-617S.
- Barst RJ, Gibbs JS, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1)(suppl):S78-S84.
- Han MK, Bach D, Hagan P, et al. Presence of right ventricular dysfunction modifies treatment response to sildenafil in the Step-IPF Trial. *Am J Respir Crit Care Med*. 2011;183: A5301.
- Han MK, Bach D, Hagan P, et al. Presence of right ventricular dysfunction predicts dyspnea and quality of life improvements with sildenafil in IPF. *Eur Respir J*. 2011;38:3S.
- Leuchte HH, Neurohr C, Baumgartner R, et al. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med*. 2004;170(4): 360-365.
- Boutou AK, Pitsiou GG, Trigonis I, et al. Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. *Respirology*. 2011;16(3):451-458.
- du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med*. 2011;183(9):1231-1237.
- Swigris JJ, Brown KK, Behr J, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med*. 2010;104(2):296-304.
- Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5:70.
- King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2008;177(1):75-81.
- King TE Jr, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;184(1):92-99.
- Ventetuolo CE, Kawut SM, Lederer DJ. Plasma endothelin-1 and vascular endothelial growth factor levels and their relationship to hemodynamics in idiopathic pulmonary fibrosis. *Respiration*. 2012;84(4):299-305.
- Nathan SD. Pulmonary hypertension in interstitial lung disease. *Int J Clin Pract Suppl*. 2008;62(160):21-28.
- Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Chest*. 2005;128(4):2393-2399.
- Han MK, McLaughlin VV, Criner GJ, Martinez FJ. Pulmonary diseases and the heart. *Circulation*. 2007;116(25): 2992-3005.